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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/744,406	01/22/2001	Michael S. Halpern	7933-38	5749

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EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,406	HALPERN ET AL.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

Re: Halpern *et al*
Priority Date: 24 July 1998

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/8/2004 has been entered.

2. Claims 1-39 are canceled without prejudice or disclaimer, and claims 40-43 are newly added. Claims 40-43 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Double Patenting – Maintained/Re-Instated

4. Upon further review and reconsideration of the claims, the previous rejection of claims 1-18 under the judicially created doctrine of obvious-type double patenting as being unpatentable over claims 1-16 of US Patent 6,365,151 (see office action mailed 7/17/2002) can now be applied to the newly added claims 40-43. Applicant responded to the rejection of 7/17/2002 in the response filed 10/21/2002, by arguing that the 6,365,151 (herein `151 patent), differs from the instantly claimed invention because the `151 patent is drawn to "autologous" cells while the claims of the instant invention are

drawn to "allogeneic" cells. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record. Because the claims of the `151 patent do not specifically exclude "allogeneic" cells or limit the cells to only "autologous" cells, the claims of the instant patent read on the `151 patent because "allogeneic" cells fall within the scope of antigen presenting cells and fibroblasts cells claimed in the prior US patent. Therefore, because the cellular immunogen taught in the `151 patent cannot be distinguished over the cellular immunogen taught in the instant application, the rejection of claims 40-43 under the judicially created doctrine of obvious-type double patenting is maintained.

New Arguments

Claim Rejections - 35 USC § 112, 1st paragraph

5. Claims 40-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification discloses a cellular immunogen for immunizing a host against the effects of the product of a target proto-oncogene associated with cancer which comprises host cells transfected with at least one transgene construct which encodes a proto-oncogene cognate to the target proto-oncogene, a method of making a cellular immunogen comprising excising cells from a host and transfecting them with a

transgene construct, and methods of vaccinating a host against diseases comprising excising cells from a host, transfecting said cells with said transgene construct and re-introducing the cells to a host. The specification further discloses that the mutant proto-oncogene DNA is non-transforming. It is noted that the intended use of the cellular immunogen and methods of preparing a cellular immunogen of the instant invention, as clearly stated in the preamble of the claims, is for immunization of a host against cancer, which reads on vaccination of cancer.

The specification does not provide an enabling disclosure for vaccinating any host against any disease associated with the over expression of a proto-oncogene by the administration of a cellular immunogen transfected ex vivo with any transgene construct encoding any mutant proto-oncogene DNA. It is noted that while the specification discloses vaccination against any disease associated with the over expression of a proto-oncogene, neither the art at the time of filing nor the specification teach any disease related to proto-oncogene over expression other than cancer. The term "immunization" is understood in the art to mean the generation of a protective immune response against an organism or disease in a naïve or disease-free host. In the instant case, immunization against cancer implies that the mammal is prevented from developing cancer by the administration of the immunizing compounds of the instant invention. The specification provides several working examples of the instant invention.

The working examples disclose three plasmids which encode v-*src*, a fragment of v-src, or a modified chicken c-*src*. The specification further discloses that all three

oncogenes encoded by the plasmids are transforming. In addition, the working examples disclose that the subcutaneous injection in wings of chicken with any of the three *src* expressing plasmids resulted in tumors which appear to spontaneously regress over time (specification figures 1a and 1b). The working examples also demonstrate that injection of 100 μg of v-*src* plasmid followed 5 weeks later by a second injection of 200 μg of c-*src* plasmid results in decreased percentage of chickens with palpable tumors compared to control animals that received a single *src*-plasmid injection. It is noted that the specification does not present any data concerning the removal and transfection of any types of cells, such as fibroblasts from host animals with any oncogene encoding constructs, or the demonstration that the re-introduction of a cellular immunogen following transfection with a construct encoding an altered or mutated proto-oncogene resulted in the protection from tumor challenge or from spontaneous tumor formation. Applicant's working examples fail to demonstrate the generation of any src-specific immune response, such as src-specific CTL or antibodies, in the animal either by direct injection of the *src* plasmids or with cells transfected with *src*-plasmids. As noted above, a single injection with the *src*-plasmid results in the tumor formation with regression over a period of weeks. The challenge experiments show the same effects of increased tumor formation followed by regression. Thus the experiments clearly do not demonstrate immunity to cancer as the second *src*-plasmid injection clearly results in initial tumor growth. Further, since the specification does not provide data correlating the tumor regression with *src*-specific immune response, it is unclear whether the tumor regression is caused by immune reactivity or by loss of

expression of the transforming *src*-protein. At the time of filing, Verma *et al* (Nature, 1997; 389:239-242) teach that "[t]he Achilles heel of gene therapy is gene delivery.." and that most of the current approaches, ".. suffer from poor efficiency of delivery and transient expression of the gene" (see page 239, col.3, paragraph 2). With regards to expression of the genes, Verma *et al* cites examples of an *ex vivo* gene therapy attempt where a retrovirus was used to express factor IX in fibroblast which were then grafted into an immunocompromised murine host. According to Verma *et al*, "within five to seven days of transplanting the infected cells back into mice, expression of factor IX is shut off", and that appropriate enhancer-promoter combinations are necessary to override the 'off switch'. Verma concludes by stating that "the search for such combinations is a case of trial and error for a given cell type" (see page 240). Thus the skilled artisan would not perceive the data provided as correlative that the methods, cells, and transgene constructs disclosed by the specification were enabling for the vaccination of mammals against cancers caused by the over expression of a proto-oncogene.

The specification does not provide sufficient guidance for generating an immune response against a proto-oncogene using any route of delivery, any oncogene constructs, and any dosage of cells transfected with oncogene constructs or the oncogene constructs themselves, or provide guidance as to the level and duration of transgene expression required to generate and sustain a level of anti-oncogene immunity sufficient to protect against the formation of tumors caused by over expression of an oncogene. As discussed above, the art at the time of filing considered transgene

delivery and expression using all currently available vectors as unpredictable. Marshall E. (Science 1995; 269(5227):1050-1055), concurs, stating that, "difficulties in getting genes transferred efficiently to target cells -and getting them expressed- remains a nagging problem for the entire field", and that "many problems must be solved before gene therapy will be useful for more than the rare application" (see page 1054, col. 3, para. 2, and page 1055, col. 1). Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, particularly against adenoviral proteins, and the identity of the promoter used to drive gene expression. In fact, in a review of the progress of gene therapy of diseases, Freidmann (Scientific American 1997;276(6):96-101) states that "[s]o far, however, no approach, has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trails worldwide" (page 96, col. 2, para. 1).

Thus dues to the art recognized unpredictability of achieving therapeutic levels of gene expression following direct administration of nucleic acid vectors, or cells transfected with nucleic acid vectors, the lack of correlation between the specification's working examples, and the generation of *src*-specific immune response in chickens, the lack of guidance provided by the specification for the parameters affecting delivery and expression of mutated proto-oncogenes capable of generating a protective immune response against a tumor caused by oncogene over expression, and the breadth of the claims, it would have required undue experimentation to practice the instant invention as claimed and the skilled artisan would not have predicted that any and all mammals

could be vaccinated against cancer using the transgene constructs and transfected cells of the instant invention.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

7. Claims 40-43 are rejected under 35 U.S.C. 102(e) as being anticipated by Chada *et al* (US 5,693,522, filed 1/11/1995). Chada *et al* teach a cellular immunogen that is useful as an immunization product against cancer wherein the cellular immunogen comprises a cellular component that is derived from an animal (see col. 2, lines 30-46); is contacted with a vector that directs the expression of an immunogeneic component that is non-tumorigenic (which Chada *et al* define as an altered cellular component that will not cause cellular transformation or induce tumor formation – see col. 4, lines 3-5)

and is normally expressed by a tumor cell yielding an altered cellular component (see col. 2, lines 30-46), wherein the altered cellular component is includes *ras*, and *neu* (see col. 2, line 67 and col. 3, line 2). It is also taught that the cellular component can comprises a cell that is allogeneic, because it is disclosed that the cellular immunogen that is removed need not be the same animal the cell is returned (see col. 2, line 49-50). Chada *et al* also teach a method of making the cellular immunogen comprising the steps of removing a cell from an animal (as previously stated, the cell need not be the returned to the same animal from which it was derived – see col. 2, lines 49-50) and contacting the cell with a vector that expresses an immunogeneic component that is non-transforming due to alterations with the immunogeneic component, and whereint the immunogeneic component is selected from ras or neu (see col. 2, line 67 and col. 3, line 2). Chada *et al* also teach that the altered cellular component that resides within the cellular immunogen is capable of mediating an immune response (see for example col. 14, lines 59-63) and that a strong promoter is used to drive the expression of the altered cellular component within the cellular immunogen (see col. 17, lines 66, in particular).

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 40 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Gelman *et al* (Oncogene 1993; 8(11):2995-3004). Gelman *et al* teach an allogeneic cellular immunogen that comprises a proto-oncogene that is non-transforming, wherein the transgene is c-src (see abstract). Gelman *et al* further teach that the cellular immunogen was capable of eliciting an immune response against the proto-oncogene. It is noted that the claim language "for immunizing a host against the effects of the product of target proto-oncogene" found in the preamble represents an intended use of the composition. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure or composition, and where the body of the claim does not depend on the preamble for completeness but, instead, the process ste or structural limitations are able to stand alone. In re Hirao, 535 F. 2d 67, 190USPQ 15 (CCPA 1976); Kropa v. Robie, 88 USPQ 478, 481 (CCPA 1951).

All other rejections are withdrawn in view of the applicant's amendments and arguments thereto as set forth in a paper filed 7/8/2004.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1642
September 27, 2004

GARY NICKOL
PRIMARY EXAMINER

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